Remarks

The June 29, 2010 Official Action has been carefully reviewed. In view of the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

The present remarks and amendments are being filed as part of the submission required under 37 C.F.R. §1.114, in connection with the Request for Continued Examination, which is submitted concurrently herewith.

At the outset it is noted that a shortened statutory response period of three (3) months was set forth in the June 29, 2010 Official Action. Therefore, the initial due date for response is September 29, 2010.

Claims 1-4, 9, 13, 17-20, 25, and 29 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S Patent 4,906,457 in view of Japanese Patent Application JP07010772.

Claims 1-4, 9, 13, 17-20, 25, and 29 have also been rejected under 35 U.S.C §103(a) as allegedly unpatentable over Jolles et al. (Br. J. Radiol. (1966) 39:12-18) in view of the '457 patent.

The foregoing rejections constitute all of the grounds set forth in the June 29, 2010 Official Action for refusing the present application.

In accordance with the instant amendment, Applicants have amended claims 1 and 17 and added new claims 34 and 35. Support for the amendments to claims 1 and 17 can be found throughout the application including, for example, at page 6. Support for new claims 34 and 35 can be found throughout the application including, for example, at pages 6 and 26. No new matter has been introduced into this application by reason of any of the amendments presented herewith.

In view of the present amendment and the reasons set forth in this response, Applicants respectfully submit that the 35 U.S.C. §103(a) rejections of claims 1-4, 9, 13, 17-20, 25, and 29, as set forth in the June 29, 2010 Official Action,

cannot be maintained. These grounds of rejection are, therefore, respectfully traversed.

CLAIMS 1-4, 9, 13, 17-20, 25, AND 29 ARE NOT RENDEREDED OBVIOUS BY THE '457 PATENT IN VIEW OF THE '772 APPLICATION

Claims 1-4, 9, 13, 17-20, 25 and 29 have been rejected under 35 U.S.C §103(a) for allegedly unpatentable over the '457 patent in view of the '772 application. The '457 patent allegedly discloses the topical administration of soybean trypsin inhibitors for reducing the risk of skin cancer caused by sunlight or other ultraviolet radiation. The '772 application allegedly teach that soybean trypsin inhibitors include Kunitz-type soybean trypsin inhibitors. It is the Examiner's position that it would have been obvious to a skilled artisan to combine the above disclosures to arrive at the instantly claimed invention. Applicants continue to respectfully disagree with the Examiner's position for the reasons of record and those set forth below.

The instant claims are drawn to methods of reducing the risk of cutaneous tumor development and for reducing the risk of ultraviolet radiation-induced skin cancer, in skin cells that have not yet been damaged by ultraviolet radiation, comprising topical application of at least one composition containing a non-denatured soy product in an amount of from about 0.01 to about 99% by weight in a carrier, wherein the non-denatured, soy product comprises a non-denatured, Kunitz-type soybean trypsin inhibitor.

As explained in the April 7, 2010 Official Action response, the Kunitz-type soybean trypsin inhibitor is a different inhibitor than the Bowman-Birk protease inhibitor (BBI). BBI is generally characterized as a chymotrypsin inhibitor, although it inhibits both chymotrypsin and trypsin. Notably, the only soybean product exemplified by the '457 patent is BBI. Indeed, the '457 patent only teaches the anti-cancer properties of chymotrypsin inhibitors and fails to

teach or suggest the use of a trypsin specific inhibitor, such as the instantly claimed Kunitz-type soybean trypsin inhibitor, for reducing the risk of skin cancer.

Notably, ten (10) years after the '457 patent was filed (September 6, 1988), it was still the general understanding in the art that chymotrypsin inhibitors were responsible for the anti-cancer properties of soy. As evidence, Applicants previously submitted Kennedy (Amer. J. Clin. Ntr. (1998) 68:1406S-1412S). At page 3 of the instant Official Action, the Examiner states that Kennedy "appears to discuss the presence of BBIC in soybeans only in BBI. As the article is directed to BBI and BBIC, such disclosure does not suggest that BBIC is the only active agent." Applicants respectfully disagree. At the top of the right column of page 1407S, Kennedy is clearly not only talking about BBIC, which is concentrated BBI from soy extract. Indeed, Kennedy is discussing the role of soybean protease inhibitors in general. The full statement by Kennedy is: "The potential effects of the soybean protease inhibitors on rat pancreata are triggered by the ability of protease inhibitors to inhibit trypsin but not chymotrypsin, whereas the ability to inhibit carcinogenesis is associated with the ability to inhibit chymotrypsin." Clearly, there is no reference to the BBIC in this passage. Rather, this passage is referring to soybean protease inhibitors in general and is intended to provide a basis for Kennedy's argument to use BBIC as an anticarcinogenic agent.

The passage in Kennedy cites Yavelow et al. (Proc. Natl. Acad. Sci. (1985) 82:5395-5399; submitted herewith) and Kennedy et al. (Nutr. Cancer (1993) 19:281-302; Abstract provided) for support. Yavelow et al. report that "(i) a crude extract of [BBI], which can be obtained in reasonable quantities for use in animal carcinogenesis experiments, has the ability to inhibit transformation *in vitro*; (ii) other soybean protease inhibitors, or other compounds present in our crude extract, lack the ability to suppress transformation *in*

vitro" (page 5395). Indeed, Yavelow et al. conclude that their data indicate that "the chymotrypsin-inhibitory activity of the BBI is ***essential*** to suppress radiation-induced transformation *in vitro*" (page 5397; emphasis added). Moreover, Yavelow et al. state at page 5398 that:

> "trypsin-inhibitory activity is *not* essential for the suppression of radiation-induced transformation. The enzymatically modified BBI, which is only a chymotrypsin inhibitor, is still fully effective as an inhibitor of radiation-induced transformation, whereas the protease inhibitor [PI(IV)], with only trypsin-inhibitory activity, has no effect on radiation-induced transformation *in vitro*. We observed previously that ***Kunitz soybean trypsin inhibitor***, which inhibits primarily trypsin, ***has no effect on radiation-induced transformation in vitro***" (emphasis added).

Notably, Kennedy et al. support the conclusion of Yavelow et al. by stating that the anticarcinogenic activity of soybean extracts is believed to be "due to chymotrypsin inhibitor activity, which is due to the [BBI] present in the extract."

Applicants also submit herewith Messina et al. (J. Natl. Cancer Inst. (1991) 83:541-546). Messina et al. state that "soybean-derived Bowman-Birk protease inhibitor (BBI) either inhibits or prevents development of experimentally induced colon, oral, lung, liver and esophageal cancers" (page 542). Furthermore, Messina et al. teach that "the anticarcinogenic effect of the BBI is thought to stem from its ability to inhibit chymotrypsin" and that "*in vitro* comparisons of the pure BBI with an extract of soybeans containing BBI indicate that the activity of the soybean extract could be directly attributable to BBI" (page 542). In view of the foregoing, it is evident that Messina et al. teach that the anticarcinogenic properties of soybean are due only to the chymotrypsin inhibitor properties of BBI.

Applicants also submit herewith Kennedy (Pharmacol. Ther. (1998) 78:167-209). Kennedy (Pharmacol. Ther.) states that it is "clear that compounds are present in soybeans that are able to mask the ability of BBI to serve as an

anticarcinogenic agent and that are removed by various purification procedures" (page 171). Moreover, Kennedy (Pharmacol. Ther.) teaches that BBIC does not include Kunitz-type soybean trypsin inhibitor and asserts that "perhaps the most important reason for the production of a BBI-containing preparation rather than use of whole soybeans as an anticarcinogenic agent is that much of the [trypsin inhibitory] activity of the soybean extract can be removed" (page 171-172). Accordingly, Kennedy (Pharmacol. Ther.) clearly advises the skilled artisan to remove Kunitz-type soybean trypsin inhibitor from soy products to use them as anticarcinogenic against, for example, radiation-induced malignant transformation. This is a direct teaching away from the instantly claimed invention.

Accordingly, years after the filing of the '457 patent, those of skill in the art understood that the anti-cancer properties of soy were solely attributable to chymotrypsin inhibitors and not trypsin specific inhibitors, i.e., the instantly claimed Kunitz-type soybean trypsin inhibitor.

The other reference relied on by the Examiner, the '772 application, only discloses that the Kunitz-type soybean trypsin inhibitor suppresses increased inflammatory edema. There is no teaching or suggestion that the Kunitz-type soybean trypsin inhibitor reduces the risk of cutaneous tumor development in skin cells that have not yet been damaged by ultraviolet radiation or reduces the risk of ultraviolet radiation-induced skin cancer in skin cells that have not been damaged by ultraviolet radiation, when administered topically, as instantly claimed.

In addition to all of the above, the instant application provides data that the Kunitz-type soybean trypsin inhibitor and soy product which has not been denatured (e.g., not heat denatured) is unexpectedly superior to the soybean Bowman-Birk protease inhibitor and denatured soy product (see, e.g., Table 1 and Figures 1, 2, and 4 of U.S. Patent

Application No. 10/108,248). At pages 3-4 of the instant Official Action, the Examiner contends that "the difference in tumor volume per mouse between no treatment and STI without taking error rates into consideration is only a few mm^3 which does not suggest an unexpected result." Applicants respectfully disagree. As explained in Table 1, the Kunitz-type soybean trypsin inhibitor was administered in liposomes. Accordingly, the proper comparison would be against empty liposome data. As seen in Figure 1 and Table 1, the presence of the Kunitz-type soybean trypsin inhibitor significantly (and unexpectedly) reduced the percentage of mice with tumors, the number of tumors per mouse, and the volume per tumor compared to liposome controls. Moreover, Figure 2 and Table 1 also demonstrate that non-denatured soymilk (aqueous solution comprising active Kunitz-type soybean trypsin inhibitor) significantly (and unexpectedly) reduced the percentage of mice with tumors, the number of tumors per mouse, and the volume per tumor compared to heated soymilk (wherein the Kunitz-type soybean trypsin inhibitor is denatured).

In view of all of the foregoing, it is clear that the instant rejection of claims 1-4, 9, 13, 17-20, 25, and 29 under 35 U.S.C §103(a) is untenable. Withdrawal of the rejection is respectfully requested.

CLAIMS 1-4, 9, 13, 17-20, 25, AND 29 ARE NOT RENDEREDED OBVIOUS BY JOLLES ET AL. IN VIEW OF THE '457 PATENT

The Examiner has also rejected claims 1-4, 9, 13, 17-20, 25, and 29 under 35 U.S.C §103(a) as allegedly unpatentable over Jolles et al. in view of the '457 patent. Jolles et al. allegedly disclose the administration of trypsin inhibitors including soybean trypsin inhibitors to reduce the risk of skin damage due to ultraviolet radiation. The '457 patent allegedly discloses that soybean trypsin inhibitors may be administered topically. It is the Examiner's position that it would have been obvious to a skilled artisan to combine the

above disclosures to arrive at the instantly claimed invention. Applicants respectfully disagree with the Examiner's position for the reasons of record and those set forth hereinbelow.

At pages 4-5 of the instant Official Action, the Examiner states that, with regard to the instant claims, "the active steps are applying a composition which comprises a non-denatured, Kunitz-type trypsin inhibitor to skin which is not yet UV damaged." Applicants have amended claims 1 and 17 to recite that the composition is topically administered "prior to exposure of the skin to ultraviolet radiation." Accordingly, the claims actively recite the exposure to ultraviolet radiation.

In contrast to the Examiner's assertion at page 3 of the January 20, 2010 Official Action, Jolles et al. do not teach - or even suggest - the reduction in the risk of skin damage due to ultraviolet radiation. Indeed, as evidenced by page 13 and Table 2, Jolles et al. only use X-ray radiation. Specifically, Jolles et al. is concerned with "early tissue changes occurring within minutes after exposure to ionizing radiation," particularly with capillary permeability (page 12). However, UV radiation is ***non***-ionizing radiation. For example, the U.S. Department of Labor, Occupational Safety & Health Administration states that "non-ionizing radiation includes the spectrum of ultraviolet (UV)" (see, e.g., http://www.osha.gov/SLTC/radiation_nonionizing/index.html).

It is well known in the art that ionizing radiation such as X-ray radiation is very different than non-ionizing radiation such as UV radiation. For example, as explained in the instant application, subjects are exposed to UV radiation when exposed to sunlight outdoors. In contrast, X-ray exposure typically occurs only under controlled medical environments. Additionally, as explained in Example 4 of the instant application, UV radiation results in specific DNA damage such as the formation of thymine (T-T) dimers that can lead to carcinogenesis. Notably, T-T dimer formation due to

UV exposure was inhibited by topical application of non-denatured soy products comprising the Kunitz-type soybean trypsin inhibitor. However, ionizing radiation such as X-ray irradiation does not cause the formation of thymine dimers.

In view of the foregoing, it is clear that the instant claims recite exposure to UV radiation whereas the guinea pigs of Jolles et al. were only exposed to X-ray radiation. Further, Jolles et al. conclude that trypsin inhibition was not sufficient to convey protection and reduced vascular leakage to X-ray radiation as the ovomucoid trypsin inhibitor (OTI), which is specific for trypsin, failed to inhibit or reduce vascular leakage despite being administered at concentrations high enough to inhibit any local trypsin (see, e.g., Table 2 and pages 15 and 17). Based on these results, Jolles et al. conclude that "trypsin itself is not the mediator" of the ability of soy bean extracts to reduce vascular leakage (page 15, left column, second paragraph). Accordingly, even assuming *arguendo* a link between early capillary leakage and the risk of cancer development, Jolles et al. expressly ***teach away*** from the instant invention by demonstrating that trypsin inhibition had no effect on early capillary leakage.

In view of the foregoing, Jolles et al. fail to teach or suggest that non-denatured soy product can reduce risk of cutaneous tumor development in skin cells caused by UV exposure.

As explained hereinabove, the '457 patent, the other reference relied upon by the Examiner in the instant rejection, only discloses the use of a chymotrypsin inhibitor. Moreover, the general understanding in the art at the time of the instant invention was that the BBI chymotrypsin inhibitor was the sole anticarcinogenic compound of soy, as evidenced by the references previously submitted and submitted herewith. Accordingly, the references cited by the Examiner teach, in combination, that 1) trypsin is ***not*** involved in early vascular changes caused by X-ray radiation and 2) chymotrypsin

inhibitors such as the Bowman Birk inhibitor can be used to treat skin and reduce the risk of skin cancer associated with exposure to ultraviolet radiation. It is self-evident that a skilled artisan could not have combined these references to arrive at the instantly claimed methods of using the Kunitz-type soybean trypsin inhibitor to reduce the risk of cutaneous tumor development in skin cells and skin cancer induced by ultraviolet radiation.

In view of all of the foregoing, Applicants submit that the rejection of claims 1-4, 9, 13, 17-20, 25, and 29 under 35 U.S.C §103(a) cannot be reasonable maintained. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing remarks, it is respectfully urged that the rejections set forth in the June 29, 2010 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,
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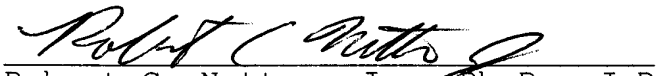
By 
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Enclosure: Safety and Health Topics by U.S. Department of Labor, Occupational Safety & Health Administration
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